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TOXICITY STUDY IN RATS

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Professor G. Sportoletti, Italfarmaco Spa, 20126 Milano, Viale Fulvio Testi 330, ITALY.

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Authors:

L. E. Fish, D. J. Lewis, C. Gopinath.

Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, ENGLAND. We the undersigned, hereby declare that the work was performed under our supervision according to the procedures herein described, and that this report provides a correct and faithful record of the results obtained.

XEtish

L. Elizabeth Fish, B.V.M.S., M.R.C.V.S., Pathologist

S. T. Leura.

David J. Lewis, B.Sc., Ph.D., M.I.Biol., M.R.C.Path., Deputy Head - Department of Pathology

lorenan

Chirukandath Gopinath, B.V.Sc., M.V.Sc., Ph.D., M.R.C.Path.,
Director of Pathology

QUALITY ASSURANCE AUDIT STATEMENT

HRC REPORT No. IFO 26/27/851445

This histopathology report has been audited by HRC Quality Assurance Unit. It is considered to be an accurate presentation of the findings.

PRILL

Peter H.C.V. Richold, B.Sc., Systems Compliance Auditor.

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Audit notes

Data are verified by means of sampling methods as described in British Standards Institution BS 6000, 6001 (1972) and US Military Standard 105D, the Acceptable Quality Level (the maximum percentage errors considered satisfactory as a process average) being 0.4.

Any computerised presentations which are the outcome of verified

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Prepared slides stained with haematoxylin and eosin or by Perls' Prussian blue method for iron together with further tissues embedded in paraffin wax were received from Italfarmaco S.p.a. Milan. The material was from Wistar rats dosed with the test compound, ITF 282, daily for 52 weeks, by oral gavage.

Histopathological examination was performed on male and female rats from control and 85~mg/kg/day ITF 282~groups killed at termination of the study.

Slides were received, stained with haematoxylin and eosin, of the following tissues:

liver spleen kidney duodenum
ileum
jejunum
caecum
colon

Additional sections stained by Perls' Prussian blue method for iron were received of the following tissues:

liver

spleen

sternum

Paraffin wax blocks were received of samples of the following tissues:

heart
actta
salivary glands
lungs
thyroids
trachea
brain
pituitary
testes
ovaries
uterus

prostate

いったとうとは、大きのでは、これに

cervical lymph nodes
 (usually salivary gland)
adrenals
pancreas
urinary bladder
seminal vesicles
stomach
Oesophagus
spinal cord
muscle
eyes

These tissues were sectioned (at HRC) at 5 μm and scained with haematoxylin and eosin.

Additional sections of lung from a proportion of rats were stained by Perls's Prussian blue method for iron.

RESULTS IFO/26/27

Individual animal histopathological findings are given in the Appendix and group lesion incidences summarised in the tables. The following comments are made in summary:

No treatment-related changes were detected.

CHANGES RELATED TO EXPERIMENTAL PROCEDURE

Minimal foci of pigmented macrophages were observed in the lungs in 3/23 male and 5/29 female rats receiving 85 mg/kg/day ITF 282 as compared with 1/32 female rats and none in male rats in the control group. Moderate foci of pigmented macrophages were recorded in 5/23 male rats and 6/29 female rats in the 85 mg/kg/day group but not in any control animals. In addition one male rat receiving 85 mg/kg/day had a single focus of pigmented macrophages.

A proportion of lung sections from these rats was stained by Perls' Prussian blue method and the pigment stained positively indicating haemosiderin.

In view of the nature of the compound and in the absence of systemic effects the most likely explanation for this pulmonary haemosiderosis is incorrect dosing during oral gavage with introduction of test compound into the lungs.

INCIDENTAL FINDINGS

41.5

Other lesions described in the individual animal reports and listed in the tables were considered spontaneous in origin and therefore of no toxicological significance.

Microscopic pathology incidence summary

			ales			Females					
	0		2		4	0	1.	2	3	4	
Animals Logged:	22	0	0	0	23	32	0	0	0	29	
Anymal notes	0	0	0	0	1	1	0	0	0	2	
Not Remarkable	0	0	0	0	0	0	0	0	0	0	
Tumour bearing rat	0	U	0	0	1	1	0	0	0	2	
Agrta	22	0	0	0	23	32	0	0	0	29	
Not Remarkable	20	0	0	0	20	28	0	O	0	24	
Misging	2	0	0	0	3	4	0	0	0	5	
Trachea	22	0	0	0	23	32	0	0	0	29	
Not Remarkable	7	0	0	0	3	12	0	0	0	4	
Missing	3	0	0	0	5	2	0	0	0	7	
Focal subepithelial mononuclear cells	1	G	0	0	0	0	0	0	0	0	
Moderate focal subepithelial mononuclear cells	1	O	0	0	0	0	0	0	0	0	
Minimal subepithelial mononuclear cells	1	0	0	0	1	0	0	0	0	0	
Subepithelial mononuclear cells	0	0	0	0	1	0	0	0	U	0	
Minimal focal subepithelial inflammation	0	0	0	0	1	0	0	0	0	0	
Moderate focal subspithelial inflammation	1	Ü	0	0	0	Q	0	0	Q	0	
Minimal subepithelial inflammation	3	0	0	0	8	10	0	0	0	16	
Moderate subepithelial inflammation	ŧ	U	0	0	4	7	0	0	0	1	
Marked subepithelial inflammation	0	0	0	0	U	0	0	0	0	1	
Inflammatory cells in lumen	1	0	0	0	1	υ	0	0	0	0	
Minimal inflammatory cults in lumen	1	U	. 0	0	0	0	0	0	0	0	
Hinimal subepithelial lymphoid aggregates	0	0	0	0	0	1	0	0	0	0	
Minimal subepithelial lymphoid hyperplasia	1	0	0	0	0	0	0	0	0	0	
Blood in lumen	2	0	0	Ü	0	0	0	0	υ	0	
Squamous metaplasia of epithelium	0	0	O	0	٥	0	0	0	0	1	
Heart	22	0	0	0	23	32	0	0	0	29	
Not Remarkable	19	0	ō	0	20	31	ō	Ü	ő	29	
Missing	2	o	0	0	3	1	o	Ü	0	- 0	
Minimal foci of myocarditis	1	0	0	ú	ō	0	0	o o	ō	o	
,				-	_	-	•	•	•	·	
Lungs	22	0	0	O	23	32	0	0	0	29	
Not Remarkable	0	9	0	0	0	0	0	0	O	0	
Missing	2	υ	0	0	2	1	υ	0	0	4	
Focus of pigmented macrophages	0	0	0	0	1	0	0	0	0	0	
Minimal foci of pigmented macrophages	0	0	0	0	3	1	0	0	0	5	
Moderate foci of pigmented macrophages	0	0	0	0	5	0	0	0	0	6	
Minimal bronchiolar epithelial hypertrophy											
with prominent goblet cells	9	0	0	0	4	11	0	0	Ü	10	
Moderate bronchiolar epithelial hypertrophy											
with prominent goblet cells	3	0	0	0	12	6	0	Ω	0	10	
Minimal peribronchiolar lymphoid aggregates	8	0	0	0	2	12	0	0	0	1.1	
Moderate peribronchiolar lymphoid aggregates .	7	0	0	0	15	15	Ð	0	C	12	
Marked focal peribronchiolar lymphoid											

TABLE

			tales			Females				
	0				4	0		2		4
Animals Logged:	22	0	0	0	23	32	0	0	0	29
Marked peribronchiolar lymphoid aggregates	Q	0	0	0	1	1	Q	0	0	0
Minimal peribronchiolar acini with										
inflammation	1	0	0	0	8	6	0	0	0	8
Moderate peribronchiolar acini with										
inflammation	1	O	Q	0	4	2	Q	0	Q	3
Bronchiectasis	0	0	0	0	2	2	0	υ	0	1
Minimal focal pnsumonitis	1	0	0	0	0	0	0	0	0	0
Focal pneumonitis	1	ō	0	0	0	D	0	0	0	0
Minimal pneumonitis	8	Q	0	0	11	16	Q	Q	0	15
Moderate pneumonitis	0	U	0	0	4	3	0	0	0	4
Focal purulent bronchopneumonia	0	0	0	0	1	0	0	0	0	0
Purulent bronchopneumonia	1	0	0	0	1	0	0	0	0	0
Bronchopneumonia	0	Ü	0	0	0	5	0	U	0	2
Pulmonary abscess(es)	0	0	0	0	2	1	0	0	0	0
Moderate persyascular mononuclear cells	1	0	0	0	0	0	0	0	0	0
Moderate alveolar congestion/haemorrhage	1	0	0	0	U	0	0	0	0	0
foci of alveolar haemorrhage	0	0	Q	0	1	G	O	0	0	1
Focal alveolar haemorrhage	0	0	0	0	1	1	0	0	0	0
Moderate alveblar haemorrhage	0	0	O	0	0	0	G	0	0	2
Minimal alveolar oudema	0	υ	0	0	0	0	0	ø	0	1
Bronchiolar haemorrhage	u	Q	0	0	1	٥	0	0	Ġ	0
Blood in bronchioles	0	0	0	0	0	1	0	0	0	0
Foci of alveolar macrophages	1	0	0	0	0	0	0	0	0	0
Focus of foamy macrophages	0	0	0	0	0	U	0	0	0	1
Minimal foci of foamy macrophages	0	0	Q	0	٥	1	G	0	٥	0
Moderate foci of foamy macrophages	0	0	0	0	2	0	0	0	0	0
Areas of foamy macrophages	0	0	0	0	1	ō	ō	0	ō	ō
Granuloma with central mineralisation	0	0	0	0	1	0	o	0	٥	0
Minimal foct of mineralisation	0	0	O	0	1	G	o.	0	0	0
rulmonary cyst not visible in sections									•	
provided	1	0	0	0	0	O	0	0	o	0
Cyst not present in sections examined	0	0	0	٥	0	٥	0	ō	υ	1
•				-	-	_	-	-	•	
Lymph nodes	22	0	0	0	23	32	a	0	0	29
Not Remarkable	2	ō	ō	ō	1	5	0	ő	o o	2
Missing	20	0	0	ō	22	27	ō	ō	Ö	26
Absceas	0	0	U	0	0	0	0	ō	0	1
	22	0	0	_				_		
ulver		-	-	0	23	32	0	0	0	29
Not Remarkable	11	0	0	0	11	20	0	0	0	17
Missing.		n	0	-	1	2	0	0	0	4
Minimal foci of mononuclear cells	4	n	0	0	4	2	0	0	0	5
Minimal periportal mononuclear cells	ם ס	0	ο	0	0	0	0	0	0	0
Minimal bile duct hyperplasia	2	o o	-	0	0	0	0	0	0	1
Focal bile duct proliferation	_	_	0	0	0	0	0	0	O	0
Focus of ground glass hepatocytes	0	0	0	0	1	0	0	0	0	0
minimal foci of ground glass nepatocytes	3	0	0	0		0	0	0	0	٥

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			Males			Females				
-	0	1 .	2		4	0	1	2	3	4
Animals Logged:	22	0	0	o	23	32	0	0	0	29
Minimal foci of basophilic hepatocytes	0	0	0	0	1	0	0	0	0	0
Focus of hypertrophic hepatocytes	C	o	0	0	o	Ô	n	0	0	1
Minimal foci of hypertrophic hepatocytes	1	0	0	0	2	0	o	a	o	0
Minimal foci of siderocytes	1	0	0	0	0	ō	ā	0	0	0
Area of fibrosis and siderocytes	1	0	0	ō	ō	o	0	Ď	ō	ō
Area of fibrosis, inflammation and adipose							•	•		
tissue	1	0	0	0	0	0	0	0	0	0
Area of mineralisation fibrosis and					-	•	•	•	-	_
onflammation	1	0	0	0	0	0	0	0	0	0
Focal periportal fibrous tissue scarring	1	U	0	Đ	0	0	0	0	o	0
Early fibrous bridging	0	0	0	0	0	0	ō	0	0	1
Focal hepatocyte necrosis	0	0	Ö	ō	ō	ō	ā	ō	ō	1
Minimal foci of hepatocyte vacuolation	0	ō	o	0	ĭ	o o	0	0	0	Ö
Minimal vacuolated hepatocytes	0	0	0	0	0	0	o	Ô	0	3
Focus of vacuolated hepatocytes	o	ō	ō	ō	1	ň	ő	0	0	0
Granuloma with central mineralisation	0	0	0	0	1	0	0	0	0	0
	-	-	-	•	•	v	٠	·	٠	·
Liver Peris'	22	0	a	0	23	32	0	O	. 0	29
Not Remarkable	2.2	0	o	ō	20	8	0	0	0	9
Missing	0	0	0	e e	1	1	0	0	i)	به م
Trace of Perls' positive material	0	o	0	a	i	Ď.	0	0	υ	0
Minimal Perls' positive material	0	0	0	0	1	0	0	0	۵	0
Trace of centrilobular Perls' positive	•	•	·	٠	:	U	U	U	U	U
material	0	G	0	٥	0	2 1	0		_	
Minimal centrilobular Perls' positive material	D	ū	0	0	0		-	0	0	16
positive material	·	·	Ū	U	U	2	0	0	0	0
Spleen	22	0	0	0	2 3	32	0	0	0	29
Not Remarkable	21	Ü	0	0	21	29	0	0	C	26
Missing	0	0	0	0	0	1	0	0	0	2
Minimal extramedullary haemopoiesis	1	0	0	0	2	2	0	0	0	1
Splean Perls'	22	u	0	0	23	32	0			• •
Not Remarkable	-0	0	0	0	0	2 2	-	Ů	0	29
Missing	Ü	υ	0	0	1	1	0	0	0	0
Trace of Peris' positive material	1	u	a	_			•	0	0	2
Minimal Perls' positive material	15	o o	t)	0	1	0	0	0	0	1
Moderate Peris' positive material	6	0	0	-	11	0	0	0	0	0
Marked Perls' positive material	0	0	-	0	10	25	0	0	U	24
nirked retis posicive material	U	U	0	0	0	6	0	0	0	2
Pancreas	22	0	0	0	23	32	0	0	0	29
Not Hemarkable	16	0	0	0	16	25	ō	Q	ŭ	16
Miasingerererererererere	2	U	0	0	4	2	ū	0	0	7
Minimal peri-islet siderocytes	1	O	0	o	0	0	0	o	o	ó
Minimal periarteritis	1	U	0	0	0	0	0	0	ō	Ü
Minimal focal inflammation	0	U	U	ŋ	1	ŭ	ŏ	ú	o	0
Executine acting atrophy	2	0	0	a	,		٥	n		

TABLE

`		м	ales			Females						
	0	1	2		4	0		2		4		
Animals Logged:	22	0	0	0	23	32	0	0	0	29		
Kidneys	22	0	0	0	23	32	0	0	0	29		
Not Remarkable	11	0	0	0	5	22	0	0	0	16		
Missing	D	0	0	0	0	ì	0	0	0	0		
Minimal foci of interstitial mononuclear cells Moderate foci of interstitial mononuclear	7	0	0	0	14	2	0	0	0	6		
cells	1	٥	0	0	1	0	0	0	0	1		
Focus of basophilic cortical tubules	2	ō	á	o o	i	ů	o	a	0	o		
Minimal foci of basophilic cortical tubules	7	ů	ő	ő	4	0	å	0	ů	ŏ		
Moderate foci of basophilic cortical tubules .	Ö	ō	Ď	ā	ï	a	ů	0	0	ā		
Focus of dilated cortical tubules with	٠	٠	·	٠	•	·	u	v	v	٠		
easinophilic contents	0	0	0	0	0	0	0	0	0	2		
Occasional dilated tubules with eosinophilic	٠	٠	٠	٠	٠	٠	٠,	. "	·	•		
contents	1	0	0	0	0	a	0	0	0	0		
Foc: of dilated cortical tubules with	•	•	٠	٠	٠	•	٠	٠	٠	·		
eosinophilic contencs	0	0	0	0	1	0	٥	0	a	0		
Minimal foci of dilated cortical tubules with	•	•	•	•	•	•	٠	Ū	v	٠		
eosinophilic contents	0	0	a	0	1	3	0	a	a	3		
Minimal progressive glomerulonephrosis	o o	0	0	٥	'n	4	o o	n	n	2		
Cortical cyst	1	o	a	0	0	0	0	0	0	0		
Peripelvic lymphoid aggregates	ò	0	0	0	0	0	8	0	0	1		
Ninimal inflammation in mesentery	٥	n	0	0	1	0	•	0	-			
MINIMAL INTLANMACION IN MESSENCETY	U	u	u	U	1	U	0	U	0	U		
Urinary bladder	22	0	0	0	23	32	0	0	0	29		
Not Remarkable	15	0	0	0	1.1	25	0	0	υ	17		
M1#610g	2	0	0	0	4	2	0	0	0	7		
Parasice(s) in lumen	4	0	0	0	6	5	O	0	0	3		
Parasitas in mucosa	2	0	0	0	0	4	0	0	0	4		
Minimal submucosal mononuclear cells	0	0	0	0	1	0	0	0	0	0		
Contains colloid	0	0	0	0	2	0	0	0	0	0		
Minimal serowal inflammation	0	0	0	0	1	0	0	0	0	0		
Uterus	0	0	0	0	0	32	0	0	0	29		
Not Remarkable	0	O	0	0	0	26	0	0	0	16		
Missing	0	0	0	0	0	1	0	0	0	5		
Eniometrial polyp	U	υ	O	0	0	1	C	0	υ	0		
Minimal squamous metaplasia of endometrial												
glands	0	U	0	0	0	2	0	0	O.	0		
Minimal dilatation of endometrial glands	0	0	0	0	0	1	0	0	0	2		
Minimal dilatation of lumen	0	0	0	0	0	0	0	0	0	5		
Moderate dilatation of lumen	n	n	0	0	0		•		•			

		Males					Females					
	0		2)	4			2	3	4		
Animals Logged.	22	0	0	.0	23	32	0	0	0	29		
Ovaries	0	0	0	0	0	32	0	0	0	29		
Not Remarkable	0	0	0	0	0	15	0	0	0	13		
Missing	0	0	0	0	0	3	0	0	0	5		
No corpora lutea	0	0	0	0	0	8	0	0	0	7		
Bilateral inflammation	0	0	0	0	0	0	0	0	0	1		
Unilateral cyst(s)	0	0	0	0	0	. 2	0	0	0	0		
Bilateral cysts	0	0	o	0	0	2	0	0	0	0		
Cyst(s)	0	0	0	0	0	0	0	0	0	1		
Unilateral parovarian cyst(s)	0	0	0	0	0	0	0	0	0	1		
Unilateral haemorrhagic cyst(s)	0	0	0	0	0	0	0	0	0	1		
Follicular cysts	0	0	0	0	0	1	0	0	0	0		
Eystic follicle(s)	0	0	0	B	0	1	0	0	0	1		
No evidence of mass in section examined	O	U	0	υ	0	1	O	0	0	0		
Prostate	22	0	0	0	23	0	0	0	0	0		
Not Hemarkable	20	0	0	0	19	0	0	0	0	0		
Missing	2	0	0	0	3	0	ō	ō	0	ō		
Focal prostatitis	0	0	0	0	1	٥	0	0	0	0		
Seminal vesicles	22	0	0	0	23	0	0	0	0	0		
Not Remarkable	20	0	0	0	19	0	0	0	0	0		
Missing	2	0	0	0	3	0	0	0	0	0		
Contracted	0	O	٥.	0	1	Đ	0	0	0	0		
Testrs	22	0	0	0	. 23	0	۵	0	0	0		
Not Kamarkable	17	O	0	0	16	0	0	0	0	0		
Missing	3	0	Ü	0	4	٥	0	0	0	0		
Moderate unilateral tubular atrophy	1	0	0	0	0	0	0	0	0	0		
focus of interstitial cell hyperplasia	1	0	0	0	0	Ö	ō	0	o	ō		
Minimal foci of interstitial cell hyperplasia .	0	υ	0	0	3	õ	0	0	0	0		
Thyroids	22	0	0	0	23	32	0	0	0	29		
Not Remarkable	20	0	0	0	15	29	0	0	0	24		
Missing	2	U	0	0	5	1	0	o	0	5		
Squamous cyst(s)	O	υ	0	υ	2	1	0	0	ō	Ö		
Manamal distended follocles	0	0	U	0	1	1	0	U	O	0		
Adrenals	22	0	0	U	23	32	0	0	0	29		
Not Remarkable	16	0	0	0	16	30	0	0	o	24		
Missing	2	O	0	0	4	1	Ü	o	ō	0		
Focus of vacuolated cortical cells	0	Ð	0	Ō	2	1	ō	ō	0	2		
Minimal congestion	0	0	0	0	0	0	0	ō	o	2		
Minimal siderocytes	0	υ	6	Ü	õ	ō	0	0	0	ī		
Focal cortical hyperplasia	2	U	0	0	1	υ	ō	ō	ā	i		
Minimal focal medullary hyperplasia	1	U	0	U	0	ō	0	0	a	0		
focal medultary hyperplasia	1	0	0	ō	ñ	n n	ñ	0	Ô	0		

TABLE (Pathology - continued)

	Males					Penales					
	0		2	3	4	0	1	2	3		
Animals Logged:	22	0	0	0	23	32	0	0	0	29	
Pituitary	22	0	0	0	23	32	0	0	0	29	
Not Remarkable	13	0	0	0	14	25	0	0	0	21	
Missing	7	0	0	0	7	4	0	0	0	7	
Cyst(s) in pars anterior	2	٥	0	0	0	0	0	0	G	0	
Focal hyperplasia in pars anterior	0	0	0	ō	ō	1	ō	ō	ō	0	
Adenoma of para anterior	ō	0	ō	ō	1		Õ	ō	ō	1	
Prominent acini and ducts in pars nervoss	0	0	ō	0	1	n	Ô	0	0	0	
Adjacent haemorrhage	ō	ō	ō	ō	0	1	ŏ	ō	ŏ	ō	
Salivary gland	22	0	0	0	23	32	0	0	0	29	
Not Remarkable	18	0	0	0	19	31	0	0	0	23	
Hissing	2	0	0	0	3	1	0	0	0	5	
Minimal foct of interstitial mononuclear cells	1	0	0	0	0	0	0	Q	Q	0	
Moderate foci of interstitial mononuclear											
cells	1	0	- Q	Q	0	0	0	0	0	0	
Minimal acini atrophy	0	0	0	0	1	0	0	0	0	0	
Minimal focal acinar atrophy	0	0	0	0	0	0	C C	0	0	1	
Oesophagus	22	o	c	0	23	32	a	0	٥	29	
Not Remarkable	17	ō	ō	o	20	30	0	o	0	23	
	Ś	0	0	0	3	2	0	0	0	6	
Hissing	,	U	U	U	3	4	U	U	U	•	
Stomach	22	0	0	0	23	32	0	0	0	29	
Not Remarkable	13	0	0	0	13	25	0	0	0	17	
Missing	2	Q	0	0 .	3	1	0	0	G	0	
Manamal mucosal inflammation(g)	3	٥	0	0	2	1	0	0	0	0	
Minimal submucosal inflammation(g)	4	0	0	0	4	C	0	0	O	0	
Minimal submucosal osdema(g)	2	0	0	Ð	0	0	0	0	0	0	
Focal submuchsal adipose tissue(g)	1	0	0	0	2	5	0	0	0	12	
Ectopic squamous epithelium(g)	0	0	0	0	1	0	0	0	0	0	
Minimal submucosal congestion(ng)	0	O	0	0	0	0	0	0	0	1	
Duodenum	22	0	0	0	23	3 2	0	0	G	29	
Not Remarkable	17	ō	0	0	20	28	0	0	0	25	
Missing	2	0	0	0	1	4	0	0	0	4	
•	3	0	6	a	-		-	-	-	-	
Minimal mucosal inflammation	,	u	U	U	2	0	0	0	0	0	
Jejunum	22	Q	0	0	23	32	0	0	0	29	
Not Remarkable	16	U	U	0	19	27	0	0	0	25	
Missing	3	0	0	0	2	3	0	0	O	4	
Minimal mucosal inflammation	2	Q	0	0	2	0	Ď	ō	ō	o	
Submicrosal lymphoid byparplagia	,	0	n	0	٥	,	•	^	•	n	

_	Males					Pemales					
-	0		2		4	0		2	3	4	
Animals Logged.	22	0	0	0	23	32	0	0	0	29	
Ileum	22	0	0	0	23	32	0	0	0	29	
Not Remarkable	18	0	0	0	16	27	0	0	0	23	
Missing	2	0	0	0	4	3	0	0	0	4	
Minimal mucosal inflammation	2	0	0	0	2	0	0	0	0	0	
Minimal lymphoid hyperplasia	U	0	0	0	1	2	0	O	0	2	
fat necrosis in mementery	0	O	O	0	U	U	0	0	U	1	
Caecum	22	0	0	0	23	32	0	0	٥	29	
Not Remarkable	10	0	0	0	15	16	0	0	υ	13	
Missing	9	0	0	0	8	10	0	0	0	8	
Parasite(s) in lumen	2	0	0	0	0	2	0	0	0	,	
Minimal mucosal inflammation	1	0	0	0	0	0	0	0	0	1	
Minimal submucosal inflammation	0	8	0	0	0	0	0	0	O	1	
Minimal submucosal oedema	0	0	0	0	0	0	0	υ	O.	1	
Minimal submucosal lymphoid hyperplasia	1	U	0	0	U	5	0	0	O	7	
Colon	22	0	0	0	23	32	0	Q	Q	29	
Not Remarkable	15	0	0	0	14	20	0	0	0	19	
Missing	2	0	0	0	2	3	0	0	0	3	
Parasite(s) in lumen	1	U	0	0	2	5	0	o	0	2	
Minimal mucosal inflammation	2	0	0	0	2	0	0	0	0	1	
Minimal submucosal inflammation	U	0	0	0	1	0	0	0	o	1	
Minimal submucosal lymphoid hyperplasia	2	0	0	0	2	4	0	0	υ	4	
Skeletal muscle	22	0	0	0	23	3 2	0	0	0	29	
Not kemarkable	12	0	0	U	19	3 1	0	0	0	23	
Missing	10	0	0	0	4	1	U	0	0	6	
Еуев	22	0	0	o	23	32	0	0	٥	29	
Nut Remarkable	18	0	O	0	18	16	0	0	0	17	
Missing	4	U	0	0	4	15	0	0	0	12	
, Arem of retinal atrophy	0	O	0	0	1	0	0	0	0	O	
Unitateral retinal atrophy	0	0	0	U	0	1	0	0	0	O	
Spinal cord	22	0	0	0	23	32	0	0	0	29	
Not Remarkable	12	0	0	0	1.5	26	0	٥	0	20	
Missing	10	0	O	0	в	6	0	0	0	9	
Brain	22	0	0	0	23	32	0	U	0	29	
Not Remarkable	18	0	o	0	20	28	0	0	0	23	

	Males							Penales					
		0		2	3	4	0	1	2	3	4		
Animals I	ogged:	22	O	0	0	23	32	0	0	0	29		
Sternum		22	0	0	0	23	32	0	0	0	29		
Not Remarkable		12	0	C C	0	20	3 1	0	0	0	23		
Missing		10	0	0	0	3	1	0	0	0	6		
Hammary gland		0	0	0	0	0	0	0	0	0	1		
Not Remarkable		0	0	0	0	0	0	0	0	0	0		
					^		^	•			•		

APPENDIX IFO/26/27

Rats killed at termination

Group: 0 1 2 3 4

Compound: - ITF 282

Level (mg/kg/day): Control 10,6 21,2 42,5 85

Histopathological findings are presented by an automated data collection system and the following comments should be noted:

The following abbreviations are used:

n.g. - non-glandular (region of stomach)

g - glandular (region of stomach)

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 2 /M

Designated: TERMINAL

The following observations were noted:

Aorta (Missing)
Trachea (Missing)
Heart (Missing)
Lungs (Missing)
Lymph nodes (Missing)

Liver Area of fibrosis and siderocytes. Focal bile duct

proliferation.

Spleen Perls' Moderate Perls' positive material.

Pancreas (Missing)

Kidneys Minimal foci of interstitial mononuclear cells.

Minimal foci of basophilic cortical tubules.

Urinary bladder (Missing) Prostate (Missing) Seminal vesicles (Missing) Testes (Missing) Thyroids (Missing) Adrenals (Missing) Pituitary (Missing) Salivary gland (Missing) Oesophagus (Missing) Stomach (Missing) Caecum (Missing) Skeletal muscle (Missing) Eyes (Missing) Spinal cord (Missing) Brain (Missing) Sternum (Missing)

The following tissues were considered normal: Liver Perls', Spleen, Duodenum, Jejunum, Ileum, Colon.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 3 /M

Designated: TERMINAL

The following observations were noted:

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Moderate peribronchiolar acini with inflammation. Minimal pneumonitis. Pulmonary cyst not

visible in sections provided.

Lymph nodes (Missing)

Spleen Perls' Minimal Perls' positive material.

Testes Moderate unilateral tubular atrophy.

Pituitary (Missing)

Stomach Minimal mucosal inflammation(g).

Caecum (Missing)
Skeletal muscle (Missing)
Spinal cord (Missing)
Sternum (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Prostate, Seminal vesicles, Thyroids, Adrenals, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Colon, Eyes, Brain.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 4 /M

Designated: TERMINAL

The following observations were noted:

Trachea Focal subepithelial mononuclear cells.

Lungs Moderate alveolar congestion/haemorrhage.

Lymph nodes (Missing)

Spleen Perls' Minimal Perls' positive material.

Kidneys Minimal foci of interstitial mononuclear cells. Focus

of basophilic cortical tubules.

Pituitary (Missing)

Stomach Minimal submucosal oedema(g).

Jejunum (Missing)
Caecum (Missing)

Colon Parasite(s) in lumen.

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Salivary gland, Oesophagus, Duodenum, Ileum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 5 /M

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial mononuclear cells.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

bronchiolar epithelial hypertrophy with prominent

goblet cells. Foci of alveolar macrophages.

Lymph nodes (Missing)

Liver Minimal periportal mononuclear cells.

Spleen Perls' Minimal Perls' positive material.

Kidneys Occasional dilated tubules with eosinophilic contents.

Testes Focus of interstitual cell hyperplasia.

Oesophagus (Missing)
Caecum (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Thyroids, Adrenals, Pituitary, Salivary gland, Stomach, Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 6 /M

Designated: TERMINAL

The following observations were noted:

Trachea Moderate focal subepithelial mononuclear cells.

Lungs Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates.

Lymph nodes (Missing)

Spleen Perls' Minimal Perls' positive material.

Pancreas Minimal peri-islet siderocytes.

Urinary bladder Parasite(s) in lumen.

Adrenals Minimal focal medullary hyperplasia.

Pituitary (Missing)
Oesophagus (Missing)

Stomach Minimal micosal inflammation(g). Minimal submucosal

oedema(g). Minimal submucosal inflammation(g).

Caecum (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Kidneys, Prostate, Seminal vesicles, Testes, Thyroids, Salıvary gland, Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Pish

Date: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 7 /M

Designated: TERMINAL

The following observations were noted:

Trachea (Missing)

Lungs Moderate peribronchiclar lymphoid aggregates. Minimal

pneumonitis. Minimal bronchiolar epithelial

hypertrophy with prominent goblet cells.

Lymph nodes (Missing

Liver Focal bile duct proliferation. Area of mineralisation

fibrosis and inflammation.

Splean Perls' Minimal Perls' positive material.

Pancreas Focal exocrine actinar atrophy.

Urinary bladder Parasite(s) in lumen.

Testes (Missing)
Duodenum (Missing)
Jejunum (Missing)
Ileum (Missing)
Caecum (Missing)
Colon (Missing)

The following tissues were considered normal:
Aorta, Heart, Liver Perls', Spleen, Kidneys, Prostate, Seminal vesicles,
Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Skeletal
muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

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(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 10 /M

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial lymphoid hyperplasia.

Lungs Minimal peribronchiolar lymphoid aggregates.

Lymph nodes (Missing)

Liver Minimal foci of ground glass hepatocytes, Minimal foci

of mononuclear cells.

Spleen Perls' Minimal Perls' positive material.

Pancreas Minimal periarteritis.

Kidneys Minimal foci of interstitial mononuclear cells.

Minimal foci of basophilic cortical tubules.

Oesophagus (Missing)
Caecum (Missing)

Colon Minimal submucosal lymphoid hyperplasia.

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Stomach, Duodenum, Jejunum, Ileum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 11 /M

Designated: TERMINAL

The following observations were noted:

Lungs Focal pneumonitis.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells.

Spleen Perls' Moderate Perls' positive material.

Urinary bladder Parasite(s) in lumen. Parasites in mucosa.

Adrenals Focus of cortical hyperplasia. Duodenum Minimal mucosal inflammation. Jejunum Minimal mucosal inflammation. Ileum Minimal mucosal inflammation.

Caecum (Missing)

Colon Minimal mucosal inflammation.

Eyes (Missing)

The following tissues were considered normal:
Aorta, Trachea, Heart, Liver Perls', Spleen, Pancreas, Kidneys, Prostate,
Seminal vesicles, Testes, Thyroids, Pituitary, Salivary gland, Oesophagus,
Stomach, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 14 /M

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation. Inflammatory cells

in lumen.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal focal pneumonitis.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Adrenals Focal medullary hyperplasia.

Colon Minimal submucosal lymphoid hyperplasia.

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 16 /M

Designated: TERMINAL

The following observations were noted:

Lungs Minimal peribronchiolar lymphoid aggregates.

Lymph nodes (Missing)

Spleen Perls' Trace of Perls' positive material.

Kidneys Minimal foci of basophilic cortical tubules.

Urinary bladder Parasite(s) in lumen.

Eyes (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Liver Perls', Spleen, Pancreas, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 17 /M

Designated: TERMINAL

The following observations were noted:

Lungs Minimal bronchiolar epithelial hypertrophy with

prominent goblet cells. Minimal peribronchiolar

lymphoid aggregates.

Lymph nodes

Liver Minimal foci of ground glass hepatocytes.

Spleen Perls' Moderate Perls' positive material.

(Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 18 /M

Designated: TERMINAL

The following observations were noted:

Lungs Minimal bronchiolar epithelial hypertrophy with

prominent goblet cells. Marked focal peribronchiolar

lymphoid aggregates.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells.

Spleen Perls' Minimal Perls' positive material.

Kidneys Minimal foci of interstitial mononuclear cells.

The following tissues were considered normal:
Aorta, Trachea, Heart, Liver Perls', Spleen, Pancreas, Urinary bladder,
Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary
gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal
muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

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(Pathology - continued)

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IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

<u>Level</u>: 0 mg/kg/day

Rat No./Sex: R 22 /M

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates.

Lymph nodes (Missing)

Liver Focal periportal fibrous tissue scarring. Minimal foci

of siderocytes.

Spleen Perls' Moderate Perls' positive material.

Stomach Focal submucosal adipose tissue(g).

Jejunum Submucosal lymphoid hyperplasia.

Caecum Parasite(s) in lumen.

Skeletal muscle (Missing)
Spinal cord (Missing)
Brain (Missing)
Sternum (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Ileum, Colon, Eyes.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 24 /M

Designated: TERMINAL

The following observations were noted:

Trachea Moderate focal subspithelial inflammation.

Lungs Minimal pneumonitis. Minimal bronchiolar epithelial

hypertrophy with prominent goblet cells. Minimal

peribronchiolar lymphoid aggregates.

Liver Minimal foci of hypertrophic hepatocytes. Area of

fibrosis, inflammation and adipose tissue.

Spleen Perls' Minimal Perls' positive material.

Duodenum Minimal mucosal inflammation.

Jejunum Minimal mucosal inflammation.

Ileum Minimal mucosal inflammation.

Caecum Minimal mucosal inflammation.

Caecum Minimal mucosal inflammation.
Colon Minimal mucosal inflammation.

Skeletal muscle (Missing)
Spinal cord (Missing)
Brain (Missing)
Sternum (Missing)

The following tissues were considered normal:

Aorta, Heart, Lymph nodes, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Eyes.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 25 /M

Designated: TERMINAL

The following observations were noted:

Trachea Minimal inflammatory cells in lumen.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal pneumonitis.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells.

Spleen Perls' Minimal Perls' positive material.

Kidneys Minimal foct of interstitual mononuclear cells.

Minimal foci of basophilic cortical tubules. Cortical

cyst.

Pituitary (Missing)
Skeletal muscle (Missing)
Spinal cord (Missing)
Sternum (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Eyes, Brain.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

0 mg/kg/day

Rat No./Sex: R

26 /M

Designated:

TERMINAL

The following observa	tions were noted:
Aorta	(Missing)
Trachea	(Missing)
Heart .	(Missing)
Lungs	(Missing)
Lymph nodes	(Missing)
Spleen Perls'	Minimal Perls' positive material.
Pancreas	(Missing)
Kidneys	Minimal foci of interstitial mononuclear cells. Focus
	of basophilic cortical tubules.
Urinary bladder	(Missing)
Prostate	(Missing)
Seminal vesicles	(Missing)
Testes	(Missing)
Thyroids	(Missing)
Adrenals	(Missing)
Pituitary	(Missing)
Salivary gland	(Missing)
Cesophagus	(Missing)
Stomach	(Missing)
Duodenum	(Missing)
Jejunum	(Missing)
Ileum	(Missing)
Caecum	(Missing)
Colon	(Missing)
Skeletal muscle	(Missing)
Eyes	(Missing)
Spinal cord	(Missing)
Brain	(Missing)
Sternum	(Missing)

The following tissues were considered normal: Liver, Liver Perls', Spleen.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 29 /M

Designated: TERMINAL

The following observations were noted:

Heart Minimal foci of myocarditis.

Lungs Minimal pneumonitis. Minimal bronchiolar epithelial

hypertrophy with prominent goblet cells.

Lymph nodes (Missing)

Spleen Perls' Minimal Perls' positive material.

Adrenals Focal cortical hyperplasia.
Pituitary Cyst(s) in pars anterior.
Duodenum Minimal mucosal inflammation.

Skeletal muscle (Missing)
Spinal cord (Missing)
Sternum (Missing)

The following tissues were considered normal:
Aorta, Trachea, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Salivary gland, Oesophagus, Stomach, Jejunum, Ileum, Caecum, Colon, Eyes, Brain.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

0 mg/kg/day

Rat No./Sex: R

30 /M

Designated:

TERMINAL

The following observations were noted:

Trachea

Minimal subepithelial inflammation.

Lungs

Moderate peribronchiolar lymphoid aggregates. Minimal

bronchiolar epithelial hypertrophy with prominent

goblet cells. Purulent bronchopneumonia.

Lymph nodes

(Missing)

Spleen Perls'

Minimal Perls' positive material.

Urinary bladder

Parasites in mucosa.

Salivary gland

Minimal foci of interstitial mononuclear cells.

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 31 /M

Designated: TERMINAL

The following observations were noted:

Trachea Blood in lumen.

Lungs Minimal peribronchiolar lymphoid aggregates. Moderate

perivascular mononuclear cells.

Lymph nodes (Missing)

Spleen Minimal extramedullary haemopoiesis.
Spleen Perls' Minimal Perls' positive material.
Pancreas Minimal exocrine acinar atrophy.

Pituitary Cyst(s) in pars anterior.

Stomach Minimal submucosal inflammation(g).

Caecum Parasite(s) in lumen. Minimal submucosal lymphoid

hyperplasia.

Skeletal muscle (Missing)
Spinal cord (Missing)
Sternum (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Kidneys, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Colon, Eyes, Brain.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 32 /M

Designated: TERMINAL

The following observations were noted:

Trachea Blood in lumen.

Lungs Minimal pneumonitis.

Spleen Perls' Minimal Perls' positive material.

Kidneys Minimal foci of basophilic cortical tubules.

Stomach Minimal mucosal inflammation(g). Minimal submucosal

inflammation(g).

Skeletal muscle (Missing)
Spinal cord (Missing)
Sternum (Missing)

The following tissues were considered normal:
Aorta, Heart, Lymph nodes, Liver, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Caecum, Colon, Eyes, Brain.

Pathologist: L.E.Fish

Date: 24 Oct85

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(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 33 /M

Designated: TERMINAL

The following observations were noted:

Lungs Minimal bronchiolar epithelial hypertrophy with

prominent goblet cells. Minimal peribronchiolar

lymphoid aggregates.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Kidneys Minimal foci of interstitial mononuclear cells.

Minimal foci of basophilic cortical tubules.

Pituitary (Missing)

Stomach Minimal submucosal inflammation(q).

Skeletal muscle (Missing)
Spinal cord (Missing)
Sternum (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Caecum, Colon, Eyes, Brain.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 37 /M

Designated: TERMINAL

The following observations were noted:

Trachea Moderate subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Munimal peribronchiolar acini with

inflammation.

Lymph nodes (Missing)

Liver Minimal foci of ground glass hepatocytes.

Spleen Perls' Minimal Perls' positive material.

Kidneys Minimal foci of basophilic cortical tubules. Moderate

foci of interstitial mononuclear cells.

Salivary gland Moderate foci of interstitial mononuclear cells.

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

ITF 282 Compound:

Level: 85 mg/kg/day

Rat No./Sex: R 201 /M

Designated: TERMINAL

The following observations were noted:

Inflammatory cells in lumen. Subepithelial mononuclear Trachea

cells.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

> pneumonitis. Minimal bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal

peribronchiolar acini with inflammation.

Lymph nodes (Missing)

Moderate Perls' positive material. Spleen Perls'

Ki dneys Moderate foci of basophilic cortical tubules.

Urinary bladder Parasite(s) in lumen. Minimal submucosal mononuclear

cells.

Caecum (Missing) Spinal cord (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Eyes, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 204 /M

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial mononuclear cells.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal pneumonitis. Minimal peribronchiolar acini with inflammation.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Kidneys Focus of basephilic cortical tubules.

Urinary bladder Parasite(s) in lumen.

Stomach Minimal mucosal inflammation(g). Minimal submucosal

inflammation(g).

Caecum (Missing)

Colon Minimal submucosal inflammation.

The following tissues were considered normal:
Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Prostate, Seminal
vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus,
Duodenum, Jejunum, Ileum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 205 /M

Designated: TERMINAL

The following observations were noted:

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Moderate peribronchiolar acini with

inflammation. Moderate pneumonitis.

Lymph nodes (Missing)

Spleen Perls' Minimal Perls' positive material.

Seminal vesicles Contracted.
Adrenals (Missing)

Stomach Minimal mucosal inflammation(g). Minimal submucosal

inflammation(g).

Duodenum Minimal mucosal inflammation.

Caecum (Missing)

Colon Minimal mucosal inflammation.

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Prostate, Testes, Thyroids, Pituitary, Salivary gland, Oesophagus, Jejunum, Ileum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

85 mg/kg/day

210 /M Rat No./Sex: R

Designated:

TERMINAL

The following observations were noted:

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

> pneumonitis. Minimal bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal

peribronchiolar acini with inflammation.

Lymph nodes

(Missing) Spleen Perls' Minimal Perls' positive material.

(Missing) Pitui tary Caecum (Missing) Spinal cord (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Eyes, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 211 /M

Designated: TERMINAL

The following observations were noted:

Trachea Minimal focal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal pneumonitis. Minimal peribronchiolar acini with inflammation.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells.

Spleen Perls' Moderate Perls' positive material.

Pancreas (Missing)

Kidneys Minimal foci of interstitial mononuclear cells.
Testes Minimal foci of interstitial cell hyperplasia.

Thyroids Minimal focus of distended follicles.

Duodenum Minimal mucosal inflammation.

Jejunum Minimal mucosal inflammation.

Caecum (Missing)
Spinal cord (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Urinary bladder, Prostate, Seminal vesicles, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Ileum, Colon, Skeletal muscle, Eyes, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

85 mg/kg/day Level:

Rat No./Sex: R 212 /M

TERMINAL Designated:

The following observations were noted:

Minimal subepithelial inflammation. Trachea

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal pneumonitis. Minimal peribronchiolar acini with inflammation.

Lymph nodes (Missing)

Minimal foci of mononuclear cells. Minimal foci of Liver

hypertrophic hepatocytes.

Spleen Perls'

Moderate Perls' positive material.
Minimal foci of interstitial mononuclear cells. Kidneys

Urinary bladder Parasite(s) in lumen.

Testes Minimal foci of interstitial cell hyperplasia.

Squamous cyst(s). Thyroids

Adrenals Focus of vacuolated cortical cells. Stomach Focus of submucosal adipose tissue(g).

(Missing) Caecum Colon (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Pancreas, Prostate, Seminal vesicles, Pituıtary, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

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IFO/26/27

Individual Animal Histopathology

ITF 282 Compound:

85 mg/kg/day Level:

Rat No./Sex: R 214 /M

TERMINAL Designated:

The following observations were noted:

Trachea (Missing)

Moderate peribronchiolar lymphoid aggregates. Moderate Lungs

bronchiolar epithelial hypertrophy with prominent goblet cells. Moderate peribronchiolar acini with

inflammation. Purulent bronchopneumonia.

Minimal foci of basophilic hepatocytes. Liver

Spleen Perls'

Moderate Perls' positive material.
Minimal foci of interstitial mononuclear cells. Kidneys

Minimal mucosal inflammation. Jejunum Ileum Minimal mucosal inflammation. Colon Minimal mucosal inflammation.

The following tissues were considered normal:

Aorta, Heart, Lymph nodes, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Caecum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 215 /M

Designated: TERMINAL

The following observations were noted:

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal pneumonitis. Minimal foci of

pigmented macrophages.

Lymph nodes (Missing)
Spleen Perls' (Missing)

Kidneys Minimal foci of interstitial mononuclear cells.

Minimal foci of basophilic cortical tubules. Foci of dilated cortical tubules with eosinophilic contents.

Caecum (Missing)
Spinal cord (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Eyes, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

ITF 282 Compound:

85 mg/kg/day Level:

216 /M Rat No./Sex: R

TERMINAL Designated:

The following observations were noted:

Animal notes Tumour bearing rat.

Trachea Minimal subepithelial inflammation.

Lungs Focal purulent bronchopneumonia. Minimal foci of

mineralisation. Bronchiectasis.

(Missing) Lymph nodes

Liver Perls' Trace of Perls' positive material. Moderate Perls' positive material. Spleen Perls'

Kidneys Minimal foci of dilated cortical tubules with

eosinophilic contents. Urinary bladder Contains colloid. Thyroids Squamous cyst(s).

Pituitary Adenoma of pars anterior [Neoplastic, Benign].

Ileum (Missing)

Colon Parasite(s) in lumen.

The following tissues were considered normal:

Aorta, Heart, Liver, Spleen, Pancreas, Prostate, Seminal vesicles, Testes, Adrenals, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Caecum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

85 mg/kg/day

Rat No./Sex: R 217 /M

Designated: TERMINAL

The following observations were noted:

Trachea

Minimal subepithelial inflammation.

Lungs

Minimal pneumonitis. Focal alveolar haemorrhage.

Bronchiolar haemorrhage. Moderate foci of pigmented

macrophages.

Lymph nodes

(Missing)

Liver

Granuloma with central mineralisation.

Spleen Perls'

Minimal Perls' positive material.

Urinary bladder

Parasite(s) in lumen.

Stomach

Minimal submucosal inflammation(g).

Ileum

(Missing)

Colon

Minimal lymphoid hyperplasia.

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Pancreas, Kidneys, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Caecum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 219 /M

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates.

Lymph nodes (Missing)

Liver Focus of ground glass hepatocytes.

Spleen Perls' Minimal Perls' positive material.

Kidneys Minimal foci of interstitial mononuclear cells.

Minimal foci of basophilic cortical tubules.

Colon Minimal lymphoid hyperplasia.

The following tissues were considered normal:
Aorta, Heart, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate,
Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland,
Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Skeletal muscle, Eyes,
Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 220 /M

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid.aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal peribronchiolar acini with inflammation. Moderate foci of pigmented macrophages.

Granuloma with central mineralisation. Pulmonary

abscess(es).

Lymph nodes (Missing)

Spleen Perls' Minimal Perls' positive material.

Pancreas Minimal focal exocrine acinar atrophy.

Pituitary Prominent acini and ducts in pars nervosa.

Jejunum (Missing)

Ileum Minimal lymphoid hyperplasia.

Eyes (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Kidneys, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Salivary gland, Oesophagus, Stomach, Duodenum, Caecum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

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IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 221 /M

Designated: TERMINAL

The following observations were noted:

Trachea (Missing)

Lungs Minimal pneumonitis. Moderate foci of pigmented

macrophages.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells.

Spleen Perls' Minimal Perls' positive material.

Kidneys Minimal foci of interstitial mononuclear cells.

Thyroids (Missing) Spinal cord (Missing)

The following tissues were considered normal:
Aorta, Heart, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate,
Seminal vesicles, Testes, Adrenals, Pituitary, Salivary gland, Oesophagus,
Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Brain,
Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

85 mg/kg/day

Rat No./Sex: R 222 /M

TERMINAL Designated:

The following observations were noted:

Minimal subepithelial inflammation.

Lungs

Moderate peribronchiolar lymphoid aggregates. Moderate bronchiolar epithelial hypertrophy with prominent goblet cells. Moderate peribronchiolar acini with

inflammation. Minimal foci of pigmented macrophages.

Bronchiectasis.

Lymph nodes

(Missing) (Missing)

Liver Liver Perls'

(Missing)

Spleen Perls'

Moderate Perls' positive material.

Pancreas

Minimal focal inflammation.

Kidneys

Minimal foci of interstitial mononuclear cells.

Minimal foci of basophilic cortical tubules.

Urinary bladder

Parasite(s) in lumen.

Pituitary

(Missing)

Colon

Parasite(s) in lumen.

The following tissues were considered normal:

Aorta, Heart, Spleen, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

Aorta

85 mg/kg/day

(Missing)

Rat No./Sex: R 223 /M

Designated: TERMINAL

The following observations were noted:

Trachea (Missing) Heart (Missing) Lungs Moderate peribronchiolar acini with inflammation. Minimal peribronchiolar lymphoid aggregates. Moderate pneumonitis. Minimal foci of pigmented macrophages. Lymph nodes (Missing) Liver Minimal foci of ground glass hepatocytes. Liver Perls' Minimal Perls' positive material. Spleen Minimal extramedullary haemopoiesis. Spleen Perls' Minimal Perls' positive material. Pancreas (Missing) Kidneys Minimal foci of interstitial mononuclear cells. Urinary bladder (Missing) Prostate (Missing) Seminal vesicles (Missing) Testes (Missing) Thyroids (Missing) Adrenals (Missing)

Pitultary (Missing) Salivary gland (Missing) Oesophagus (Missing) Stomach (Missing) Skeletal muscle (Missing) (Missing) Spinal cord (Missing) Brain (Missing) Sternum (Missing)

The following tissues were considered normal: Duodenum, Jejunum, Ileum, Caecum, Colon.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 226 /M

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

bronchiolar epithelial hypertrophy with prominent goblet cells. Moderate pneumonitis. Moderate foci of

pigmented macrophages.

Lymph nodes (Missing)

Liver Minimal foci of hepatocyte vacuolation.

Spleen Perls' Trace of Perls' positive material.

Kidneys Minimal foci of interstitial mononuclear cells.

Adrenals Focus of vacuolated cortical cells.

Pituitary (Missing)

Salivary gland Minimal acini atrophy.

Ileum Minimal mucosal inflammation.

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Testes, Thyroids, Oesophagus, Stomach, Duodenum, Jejunum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 228 /M

Designated: TERMINAL

The following observations were noted:

Trachea Moderate subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Moderate gneumonitis. Moderate foci of

ميتري

foamy macrophages.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells.

Spleen Perls' Moderate Perls' positive material.

Kidneys Minimal foci of interstitial mononuclear cells.

Minimal foci of basophilic cortical tubules.

Thyroids (Missing)
Pituitary (Missing)

Stomach Minimal submucosal inflammation(q).

Duodenum (Missing)
Jejunum (Missing)
Ileum (Missing)
Caecum (Missing)
Colon (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Testes, Adrenals, Salivary gland, Oesophagus, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 229 /M

Designated: TERMINAL

The following observations were noted:

Trachea Moderate subepithelial inflammation. .

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal pneumonitis. Focus of pigmented

macrophages.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Kidneys Minimal foci of interstitial mononuclear cells.
Testes Minimal foci of interstitial cell hyperplasia.

Adrenals Focus of cortical hyperplasia.

Eyes Area of retinal atrophy.

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Urinary bladder, Prostate, Seminal vesicles, Thyroids, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

85 mg/kg/day

Rat No./Sex: R 230 /N

Designated:

TERMINAL

The following observations were noted:

Trachea

Moderate subepithelial inflammation.

Lungs

Moderate peribronchiolar lymphoid aggregates. Minimal bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal peribronchiolar acini with inflammation. Moderate foci of foamy macrophages.

(Missing)

Lymph nodes

Liver Focus of vacuolated hepatocytes.

Spleen Perls' Minimal Perls' positive material.

Pancreas Minimal focal exocrine acinar atrophy.

Pancreas Kidneys

Minimal foci of interstitial mononuclear cells.

Minimal inflammation in mesentery.

Urinary bladder

(Missing)

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Prostate, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 231 /M

Designated: TERMINAL

The following observations were noted:

(Missing)
(Missing)
(Missing)
(Missing)
(Missing)
Moderate Perls' positive material.
(Missing)
Moderate foci of interstitial mononuclear cells.
(Missing)

The following tissues were considered normal: Liver, Liver Perls', Spleen, Duodenum, Jejunum, Ileum, Caecum, Colon.

(Missing)

Pathologist: L.E.Fish

Date: 24 Oct85

Sternum

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

TTF 282

Level:

85 mg/kg/day

Rat No./Sex: R

Designated:

TERMINAL

235 /M

The following observations were noted:

Trachea

Minimal subepithelial inflammation.

Lungs

Moderate bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal pneumonitis. Marked peribronchiolar lymphoid aggregates. Foci of alveolar

haemorrhage.

Lymph nodes

(Missing)

Spleen Perls'

Minimal Perls' positive material.

Kidneys

Minimal foci of interstitial mononuclear cells.

Urinary bladder

Minimal serosal inflammation.

Testes

(Missing)

Stomach

Ectopic squamous epithelium(g).

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Prostate, Seminal

vesicles, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain,

Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

ITF 282 Compound:

85 mg/kg/day Level:

Rat No./Sex: R 236 /M

TERMINAL Designated:

The following observations were noted:

Trachea Moderate subepithelial inflammation.

Moderate peribronchiolar lymphoid aggregates. Moderate Lungs

bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal peribronchiolar acini with inflammation. Moderate foci of pigmented macrophages.

Pulmonary abscess(es). Areas of foamy macrophages.

(Missing) Lymph nodes

Minimal foci of hypertrophic hepatocytes. Liver Spleen Minimal extramedullary haemopoiesis.

Spleen Perls' Minimal Perls' positive material.

Kidneys Minimal foci of interstitual mononuclear cells.

Urinary bladder Parasite(s) in lumen. Contains colloid.

Prostate Focal prostatitis.

Focal submucosal adipose tissue(g). Stomach

Skeletal muscle (Missing)

The following tissues were considered normal: Aorta, Heart, Liver Perls', Pancreas, Seminal vesicles, Testes, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum,

Caecum, Colon, Eyes, Spinal cord, Brain, Sternum,

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No . / Sex: R 243 /M

Designated: TERMINAL

The following observations were noted: (Missing) Aorta (Missing) Trachea (Missing) Heart (Missing) Lungs (Missing) Lymph nodes Minimal Perls' positive material. Spleen Perls' (Missing) Pancreas (Missing) Urinary bladder (Missing) Prostate (Missing) Seminal vesicles Testes (Missing) (Missing) Thyroids Adrenals (Missing) (Missing) Pitultary Salivary gland (Missing) (Missing) Oesophagus (Missing) Stomach (Missing) Ileum (Missing) Skeletal muscle (Missing) Eyes Spinal cord (Missing) Brain (Missing) (Missing) Sternum

The following tissues were considered normal: Liver, Liver Perls', Spleen, Kidneys, Duodenum, Jejunum, Caecum, Colon.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 252 /F

Designated: TERMINAL

The following observations were noted:

Lungs Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells.

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Caecum (Missing) Eyes (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Spleen, Pancreas, Kidneys, Urinary bladder, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

0 mg/kg/day

Rat No./Sex: R

Designated:

TERMINAL

253 /F

The following observations were noted:

Trachea

Moderate subepithelial inflammation.

Lungs

Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates.

Lymph nodes

(Missing)

Liver Perls'

Trace of centrilobular Perls' positive material.

Spleen Perls'

Moderate Perls' positive material.

Kidneys

Minimal foci of dilated cortical tubules with

eosinophilic contents.

Adrenals

Focus of vacuolated cortical cells.

Caecum

(Missing)

The following tissues were considered normal:
Aorta, Heart, Liver, Spleen, Pancreas, Urinary bladder, Uterus, Ovaries,
Thyroids, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum,
Ileum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 254 /F

Designated: TERMINAL

The following observations were noted:

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

pneumonitis. Minimal bronchiolar epithelial

hypertrophy with prominent goblet cells. Minimal foci

of pigmented macrophages.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Thyroids Squamous cyst(s).

Caecum (Missing)

The following tissues were considered normal:
Aorta, Trachea, Heart, Liver, Spleen, Pancreas, Kidneys, Urinary bladder,
Uterus, Ovaries, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach,
Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain,
Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

TTF 282

Level:

0 mg/kg/day

Rat No./Sex: R 255 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Minimal bronchiolar epithelial hypertrophy with

prominent goblet cells. Minimal peribronchiolar

lymphoid aggregates.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Ovaries Unilateral cyst(s).

Duodenum (Missing)

Ileum Minimal lymphoid hyperplasia.

Caecum (Missing)

The following tissues were considered normal:
Aorta, Heart, Liver, Spleen, Pancreas, Kidneys, Urinary bladder, Uterus,
Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Jejunum,
Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 256 /F

Designated: TERMINAL

The following observations were noted:

Lungs Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates. Minimal foci of foamy macrophages.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells.

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Kidneys Munimal foci of interstitial mononuclear cells.

Pituitary (Missing)
Caecum (Missing)

Colon Minimal lymphoid hyperplasia.

Brain (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Spleen, Pancreas, Urinary bladder, Uterus, Ovaries, Thyroids, Adrenals, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Skeletal muscle, Eyes, Spinal cord, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

· IFO/26/27

Individual Animal Histopathology

ITF 282 Compound:

0 mg/kg/day Level:

Rat No./Sex: R 258 /F

TERMINAL Designated:

The following observations were noted:

Lungs Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls'

Moderate Perls' positive material.
Minimal foci of dilated cortical tubules with Kidneys

eosinophilic contents.

Urinary bladder (Missing)

Caecum (Missing)

Colon Minimal lymphoid hyperplasia.

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Spleen, Pancreas, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 259 /F

Designated: TERMINAL

The following observations were noted:

Lungs Minimal peribronchiolar lymphoid aggregates.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Marked Perls' positive material.

Duodenum (Missing)
Jejunum (Missing)
Ileum (Missing)
Caecum (Missing)
Colon (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Spleen, Pancreas, Kidneys, Urinary bladder, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 260 /F

Designated: TERMINAL

The following observations were noted:

Lungs Minimal peribronchiolar lymphoid aggregates. Focal

alveolar haemorrhage. Blood in bronchioles.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Kidneys Minimal progressive glomerulonephrosis.

Ovaries No corpora lutea.

Thyroids Minimal distended follicles.

Pituitary Focal hyperplasia in pars anterior.

Oesophagus (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Liver Perls', Spleen, Pancreas, Urinary bladder, Uterus, Adrenals, Salivary gland, Stomach, Duodenum, Jejunum, Ileum, Caecum,

Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 262 /F

Designated: TERMINAL

The following observations were noted:

Trachea Moderate subepithelial inflammation.

Lungs Marked peribronchiolar lymphoid aggregates.

Bronchopneumonia.

'Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Marked Perls' positive material.

Uterus Endometrial polyp.
Pituitary Adjacent haemorrhage.

Colon Minimal lymphoid hyperplasia.

The following tissues were considered normal:

Aorta, Heart, Lymph nodes, Liver, Spleen, Pancreas, Kidneys, Urinary bladder, Ovaries, Thyroids, Adrenals, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 264 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial lymphoid aggregates.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

bronchiolar epithelial hypertrophy with prominent

goblet cells.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Pancreas Minimal focal exocrine acinar atrophy.

Kidneys Minimal progressive glomerulonephrosis.

Urinary bladder Parasite(s) in lumen. Parasites in mucosa.

Ovaries No corpora lutea. Follicular cysts.

Pituitary (Missing) Spinal cord (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Spleen, Uterus, Thyroids, Adrenals, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

ITF 282 Compound:

0 mg/kg/day Level:

265 /F Rat No./Sex: R

TERMINAL Designated:

The following observations were noted:

Animal notes Tumour bearing rat.

Minimal subepithelial inflammation. Trachea

Moderate peribronchiolar lymphoid aggregates. Moderate Lungs bronchiolar epithelial hypertrophy with prominent

goblet cells. Moderate peribronchiolar acini with

inflammation. Bronchopneumonia.

(Missing) Lymph nodes Liver (Missing) (Missing) Liver Perls'

Marked Perls' positive material. Spleen Perls'

Ovaries Bilateral cysts.

Adenoma of pars anterior [Neoplastic, Benign]. Pituitary

Foci of submucosal adipose tissue(g). Stomach

The following tissues were considered normal:

Aorta, Heart, Spleen, Pancreas, Kidneys, Urinary bladder, Uterus, Thyroids, Adrenals, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

0 mg/kg/day

Rat No./Sex: R

266 /F

Designated:

TERMINAL

The following observations were noted:

Trachea Moderate subepithelial inflammation.

Lungs Minimal pneumonitis. Minimal bronchiolar epithelial

hypertrophy with prominent goblet cells. Minimal

peribronchiolar lymphoid aggregates.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Kidneys Minimal foci of dilated cortical tubules with

eosinophilic contents.

Urinary bladder Parasite(s) in lumen. Parasites in mucosa.

Uterus Moderately dilated.

Stomach Foci of submucosal adipose tissue(g).

The following tissues were considered normal:

Aorta, Heart, Liver, Spleen, Pancreas, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Byes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 268 /F

Designated: TERMINAL

The following observations were noted:

Trachea Moderate subepithelial inflammation.

Lungs Minimal bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal peribronchiolar

prominent gobiet cells. Minimal peribronchiolar lymphoid aggregates. Minimal peribronchiolar acini

with inflammation. Bronchopneumonia.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Uterus Minimal squamous metaplasia of endometrial glands.

Ovaries No evidence of mass in section examined.

The following tissues were considered normal:

Aorta, Heart, Liver, Spleen, Pancreas, Kidneys, Urinary bladder, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 270 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Minimal bronchiolar epithelial hypertrophy with

prominent goblet cells. Minimal peribronchiolar lymphoid aggregates. Minimal peribronchiolar acini

with inflammation.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Pancreas Minimal focal exocrine acinar atrophy.

Stomach Foci of submucosal adipose tissue(g).

Caecum Minimal lymphoid hyperplasia.

Colon Parasite(s) in lumen.

Brain (Missing)

The following tissues were considered normal:
Aorta, Heart, Liver, Spleen, Kidneys, Urinary bladder, Uterus, Ovaries,
Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum,
Ileum, Skeletal muscle, Eyes, Spinal cord, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 271 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

pneumonitis.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Ovaries No corpora lutea.

Eyes Unilateral retinal atrophy.

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Uterus, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 272 /F

Designated: TERMINAL

The following observations were noted:

Trachea Moderate subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal peribronchiolar acini with

inflammation. Moderate pneumonitis.

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Stomach Foci of submucosal adipose tissue(g).

The following tissues were considered normal:
Aorta, Heart, Lymph nodes, Liver, Spleen, Pancreas, Kidneys, Urinary bladder,
Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus,
Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord,
Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 273 /F

Designated: TERMINAL

The following observations were noted:

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

pneumonitis. Minimal bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal

peribronchiolar acıni with inflammation.

Liver Perls' Minimal centrilobular Perls' positive material.

Spleen Perls' Marked Perls' positive material.

Urinary bladder Parasite(s) in lumen. Parasites in mucosa.

Ovaries No corpora lutea.

Pituitary (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Lymph nodes, Liver, Spleen, Pancreas, Kidneys, Uterus, Thyroids, Adrenals, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Byes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 274 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

pneumonitis. Minimal bronchiolar epithelial hypertrophy with prominent goblet cells.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Uterus Minimal squamous metaplasia of endometrial glands.

Ovaries (Missing) Spinal ∞ rd (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Spleen, Pancreas, Kidneys, Urinary bladder, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 275 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal pneumonitis. Minimal

peribronchiolar acini with inflammation.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.
Pancreas Minimal focal exocrine acinar atrophy.

Duodenum (Missing)
Jejunum (Missing)
Ileum (Missing)
Caecum (Missing)
Colon (Missing)
Eyes (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Kidneys, Urinary bladder, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 277 /F

Designated: TERMINAL

The following observations were noted:

Lungs Pulmonary abscess(es). Bronchiectasis.

Bronchopneumonia.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Ovaries No corpora lutea.
Colon Parasite(s) in lumen.

Eyes (Missing)
Spinal cord (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Uterus, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Skeletal muscle, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 278 /F

Designated: TERMINAL

The following observations were noted:

Aorta (Missing)

· Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

bronchiolar epithelial hypertrophy with prominent

goblet cells.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Minimal extramedullary haemopoiesis.
Spleen Perls' Moderate Perls' positive material.

Ovaries (Missing)
Caecum Minimal lymphoid hyperplasia.

Eyes (Missing)
Brain (Missing)

The following tissues were considered normal:

Trachea, Heart, Liver, Pancreas, Kidneys, Urinary bladder, Uterus, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Spinal cord, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 279 /F

Designated: TERMINAL

The following observations were noted:

Aorta (Missing)

Trachea Moderate subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

pneumonitis. Minimal bronchiolar epithelial hypertrophy with prominent goblet cells.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Eyes (Missing) Spinal cord (Missing)

The following tissues were considered normal:

Heart, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 280 /F

Designated: TERMINAL

The following observations were noted:

Aorta (Missing) Trachea (Missing) (Missing) Heart (Missing) Lungs Lymph nodes (Missing) (Missing) Liver Spleen (Missing) Spleen Perls' (Missing) Pancreas (Missing) Kidneys (Missing) Urinary bladder (Missing) Uterus (Missing) Ovaries (Missing) Thyroids (Missing) Adrenals (Missing) Pituitary (Missing) Salivary gland (Missing) Oesophagus (Missing) Stomach (Missing) Duodenum (Missing) Jejunum (Missing) Ileum (Missing) Caecum (Missing) Colon (Missing) Skeletal muscle (Missing) Eyes (Missing) Spinal cord (Missing) Brain (Missing) Sternum (Missing)

The following tissues were considered normal: Liver Perls'.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 281 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

pneumonitis.

Spleen Perls' Moderate Perls' positive material.

Kidneys Minimal progressive glomerulonephrosis.

Urinary bladder Parasite(s) in lumen.
Ovaries Unilateral cyst(s).
Caecum Parasite(s) in lumen.

Eyes (Missing)

The following tissues were considered normal:
Aorta, Heart, Lymph nodes, Liver, Liver Perls', Spleen, Pancreas, Uterus,
Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum,
Jejunum, Ileum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 283 /F

Designated: TERMINAL

The following observations were noted:

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

bronchiolar epithelial hypertrophy with prominent

goblet cells. Moderate pneumonitis.

Lymph nodes (Missing)

Liver Perls' Minimal centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Pancreas (Missing)

Ovaries No corpora lutea.

Caecum (Missing)

Colon Parasite(s) in lumen.

Eyes (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Spleen, Kidneys, Urinary bladder, Uterus, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum,

Jejunum, Ileum, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 284 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs . Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates.

'Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Marked Perls' positive material.
Pancreas Pocal exocrine acinar atrophy.

Urinary bladder Parasite(s) in lumen. Parasites in mucosa.

Ovaries Bilateral cysts.

Jejunum Minimal lymphoid hyperplasia. Caecum Minimal lymphoid hyperplasia.

Eyes (Missing)

The following tissues were considered normal:
Aorta, Heart, Lymph nodes, Liver, Spleen, Kidneys, Utdrus, Thyroids, Adrenals,
Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Ileum, Colon,
Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 285 /F

Designated: TERMINAL

The following observations were noted:

Trachea Moderate subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal pneumonitis. Minimal peribronchiolar acini with inflammation.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Ovaries Cystic follicle(s).

Caecum Parasite(s) in lumen. Minimal lymphoid hyperplasia.

Eyes (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Spleen, Pancreas, Kidneys, Urinary bladder, Uterus, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

ITF 282 Compound:

0 mg/kg/day Level:

Rat No./Sex: R 286 /F

Designated: TERMINAL

The following observations were noted:

(Missing) Trachea

Minimal pneumonitis. Lungs

Lymph nodes (Missing)

Trace of centrilobular Perls' positive material. Liver Perls'

Minimal extramedullary haemopoiesis. Spleen

Spleen Perls'

Moderate Perls' positive material.
Minimal foci of interstitial mononuclear cells. Kidneys

Minimal lymphoid hyperplasia. Caecum

(Missing) Eyes

The following tissues were considered normal:

Aorta, Heart, Liver, Pancreas, Urinary bladder, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum,

Ileum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 287 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal pneumonitis.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Pancreas Minimal focal exocrine acinar atrophy.

Colon Parasite(s) in lumen.

Eyes (Missing)

The following tissues were considered normal:
Aorta, Heart, Liver, Spleen, Kidneys, Urinary bladder, Uterus, Ovaries,
Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum,
Jejunum, Ileum, Caecum, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 0 mg/kg/day

Rat No./Sex: R 288 /F

Designated: TERMINAL

The following observations were noted:

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Moderate peribronchiolar acini with

inflammation. Bronchopneumonia.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Stomach Minimal mucosal inflammation(g).

Jejunum Minimal lymphoid hyperplasia.

Ileum Minimal lymphoid hyperplasia.

Colon Parasite(s) in lumen.

Eyes (Missing) Spinal cord (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Spleen, Pancreas, Kidneys, Urinary bladder, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Caecum, Skeletal muscle, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

0 mg/kg/day

Rat No./Sex: R

289 /F

Designated:

TERMINAL

The following observations were noted:

Lungs

Bronchiectasis.

Lymph nodes

(Missing)

Liver Perls'

Trace of centrilobular Perls' positive material.

Spleen Perls'

Moderate Perls' positive material.

Uterus

Minimal dilatation of endometrial glands.

Ovaries

No corpora lutea.

Stomach

Foci of submucosal adipose tissue(g).

Colon

Minimal lymphoid hyperplasia.

Eyes

(Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Spleen, Pancreas, Kidneys, Urinary bladder, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Caecum, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

TTF 282

Level:

0 mg/kg/day

Rat No./Sex: R

290 /F

Designated:

TERMINAL

The following observations were noted:

Aorta

(Missing)

Trachea

Minimal subepithelial inflammation.

Lungs

1

Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates.

Lymph nodes

(Missing)

Spleen Perls'

Marked Perls' positive material.

Kidneys

Minimal progressive glomerulonephrosis.

Ovaries

No corpora lutea.

Eyes

(Missing)

The following tissues were considered normal:

Heart, Liver, Liver Perls', Spleen, Pancreas, Urinary bladder, Uterus,

Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 451 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal peribronchiolar acini with inflammation. Moderate pneumonitis. Moderate foci of

pigmented macrophages.

Lymph nodes (Missing)
Liver (Missing)
Liver Perls' (Missing)
Spleen (Missing)
Spleen Perls' (Missing)

Kidneys Minimal foci of interstitial mononuclear cells.

Ovaries No corpora lutea.
Adrenals Minimal congestion.

Duodenum (Missing)
Jejunum (Missing)
Ileum (Missing)
Caecum (Missing)
Colon (Missing)
Spinal cord (Missing)

The following tissues were considered normal:

Aorta, Heart, Pancreas, Urinary bladder, Uterus, Thyroids, Pituitary, Salivary gland, Oesophagus, Stomach, Skeletal muscle, Eyes, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 453 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Minimal pneumonitis. Minimal bronchiolar epithelial

hypertrophy with prominent goblet cells. Minimal

peribronchiolar lymphoid aggregates.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells.

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Uterus Minimal dilatation of lumen.
Ovaries Unilateral parovarian cyst(s).

Caecum (Missing)

Colon Parasite(s) in lumen.

The following tissues were considered normal:

Aorta, Heart, Spleen, Pancreas, Kidneys, Urinary bladder, Thyroids, Adrenals, Piturtary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 454 /F

Designated: TERMINAL

The following observations were noted:

Trachea Marked subepithelial inflammation. Squamous metaplasia

of epithelium.

Lungs Moderate bronchiolar epithelial hypertrophy with

prominent goblet cells. Moderate peribronchiolar acini

with inflammation. Bronchopneumonia.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Urinary bladder Parasite(s) in lumen.

Stomach Foci of submucosal adipose tissue(g).

Duodenum (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Spleen, Pancreas, Kidneys, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 457 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Moderate peribronchiolar acini with inflammation. Minimal pneumonitis. Minimal foci of

pigmented macrophages.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.
Pancreas Focal exocrine acinar atrophy.
Stomach Foci of submucosal adipose tissue(g).

Caecum (Missing)

Colon Minimal lymphoid hyperplasia.

Spinal cord (Missing)
Sternum (Missing)

The following tissues were considered normal:
Aorta, Heart, Liver, Spleen, Kidneys, Urinary bladder, Uterus, Ovaries,
Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum,

Ileum, Skeletal muscle, Eyes, Brain.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 458 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.
Lungs Bronchiectasis. Bronchopneumonia.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells.

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Kidneys Minimal foci of interstitial mononuclear cells.

Adrenals Minimal congestion. Minimal siderocytes.

Jejunum (Missing)

Ileum Minimal lymphoid hyperplasia.

Caecum (Missing)

The following tissues were considered normal:
Aorta, Heart, Spleen, Pancreas, Urinary bladder, Uterus, Ovaries, Thyroids,
Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Colon, Skeletal

muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 459 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Minimal bronchiolar epithelial hypertrophy with

prominent goblet cells. Minimal peribronchiolar

lymphoid aggregates.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells. Focal hepatocyte

necrosis.

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Kidneys Minimal foci of interstitial mononuclear cells.

Urinary bladder Parasite(s) in lumen. Parasites in mucosa.

Adrenals Focus of cortical hyperplasia.
Salivary gland Minimal focal acinar atrophy.

Caecum (Missing)

The following tissues were considered normal:
Aorta, Heart, Spleen, Pancreas, Uterus, Ovaries, Thyroids, Pituitary,
Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Eyes,
Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 460 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal peribronchiolar acini with

inflammation. Moderate pneumonitis.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Minimal extramedullary haemopoiesis.

Spleen Perls' Moderate Perls' positive material.

Uterus Minimal dilatation of lumen.

Ovaries Bilateral inflammation.

Ileum Minimal lymphoid hyperplasia. Fat necrosis in

mesentery.

Caecum Minimal lymphoid hyperplasia.

The following tissues were considered normal:
Aorta, Heart, Liver, Pancreas, Kidneys, Urinary bladder, Thyroids, Adrenals,
Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Colon,
Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: . ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 461 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal peribronchiolar

lymphoid aggregates. Minimal peribronchiolar acini with inflammation. Moderate pneumonitis. Minimal foci of pigmented macrophages. Focus of foamy macrophages.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Ovaries Unilateral haemorrhagic cyst(s). Cyst(s).

Oesophagus (Missing) Eyes (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Uterus, Thyroids, Adrenals, Pituitary, Salivary gland, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 462 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Minimal pneumonitis. Minimal bronchiolar epithelial

hypertrophy with prominent goblet cells. Minimal peribronchiolar lymphoid aggregates. Moderate foci of

pigmented macrophages.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Uterus Minimal dilatation of lumen.

Stomach Foci of submucosal adipose tissue(g).

Ileum (Missing) Skeletal muscle (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Spleen, Pancreas, Kidneys, Urinary bladder, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Caecum, Colon, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

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(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 464 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

pneumonitis. Minimal bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal

peribronchiolar acini with inflammation.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Pancreas Minimal focal exocrine acinar atrophy.

Uterus Minimal dilatation of endometrial glands.

Ovaries No corpora lutea.

Caecum Minimal lymphoid hyperplasia.

The following tissues were considered normal:
Aorta, Heart, Liver, Spleen, Kidneys, Urinary bladder, Thyroids, Adrenals,
Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum,

Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 465 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs . Minimal bronchiolar epithelial hypertrophy with

prominent goblet cells. Minimal peribronchiolar

lymphoid aggregates.

Lymph nodes (Missing)

Liver Minimal vacuolated hepatocytes.

Spleen Perls' Moderate Perls' positive material.

Pancreas Minimal focal exocrine acinar atrophy.

Kidneys Minimal progressive glomerulonephrosis.

Uterus Minimal dilatation of lumen.

Ovaries No corpora lutea.

The following tissues were considered normal:

Aorta, Heart, Liver Perls', Spleen, Urinary bladder, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

<u>Date</u>: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: . TTF 282

85 mg/kg/day Level:

Rat No./Sex: R 466 /F

TERMINAL Designated:

The following observations were noted:

Animal notes Tumour bearing rat.

Moderate subepithelial inflammation. Trachea

Moderate peribronchiolar lymphoid aggregates. Moderate Lungs

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal pneumonitis. Minimal

peribronchiolar acini with inflammation. Minimal foci

of pigmented macrophages.

(Missing) Lymph nodes

Spleen Perls' Moderate Perls' positive material.

Pancreas (Missing)

Minimal foci of interstitial mononuclear cells. Kidneys

Minimal foci of dilated cortical tubules with

eosinophilic contents.

Urinary bladder Parasites in mucosa.

(Missing) Pituitary

Spinal cord (Missing)

Mammary fibroadenoma [Neoplastic, Benign]. Mammary gland

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Uterus, Ovaries, Thyroids, Adrenals, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Brain, Sternum.

Pathologist: L.E.Pish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 467 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal pneumonitis. Minimal

peribronchiolar acini with inflammation. Moderate foci

of pigmented macrophages.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Urinary bladder Parasite(s) in lumen. Parasites in mucosa.
Uterus Minimal dilatation of endometrial glands.

Caecum Minimal lymphoid hyperplasia.

Colon Parasite(s) in lumen.

The following tissues were considered normal:
Aorta, Heart, Liver, Spleen, Pancreas, Kidneys, Ovaries, Thyroids, Adrenals,
Pituitary, Salivary gland, Ossophagus, Stomach, Duodenum, Jejunum, Ileum,
Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

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(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 468 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal peribronchiclar acini with inflammation. Moderate pneumonitis. Moderate foci of

pigmented macrophages.

Spleen Perls' Trace of Perls' positive material.

Pancreas Minimal focal exocrine acinar atrophy.

Urinary bladder Parasites in mucosa.

Uterus Minimal dilatation of lumen.

Adrenals Focus of vacuolated cortical cells.

The following tissues were considered normal:

Aorta, Heart, Lymph nodes, Liver, Liver Perls', Spleen, Kidneys, Ovaries, Thyroids, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

ITF 282 Compound:

85 mg/kg/day Level:

470 /F Rat No./Sex: R

TERMINAL Designated:

The following observations were noted:

Tumour bearing rat. Animal notes

Trachea (Missing)

Moderate peribronchiolar lymphoid aggregates. Moderate Lungs

bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal pneumonitis. Minimal foci of

pigmented macrophages.

(Missing) Lymph nodes

Minimal foci of mononuclear cells. Minimal vacuolated Liver

hepatocytes.

Trace of centrilobular Perls' positive material. Liver Perls'

Moderate Perls' positive material. Spleen Perls' . Kidneys Minimal progressive glomerulonephrosis.

Adenoma of pars anterior [Neoplastic, Benign]. Pituitary

Stomach Foci of submucosal adipose tissue(g). Minimal

submucosal congestion(ng).

Caecum Parasite(s) in lumen. Minimal lymphoid hyperplasia.

The following tissues were considered normal:

Aorta, Heart, Spleen, Pancreas, Urinary bladder, Uterus, Ovaries, Thyroids, Adrenals, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Colon, Skeletal muscle, Eyes, Spinal ord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 471 /F

Designated: TERMINAL

The following observations were noted:

Lungs Moderate peribronchiolar lymphoid aggregates. Minimal

pneumonitis. Cyst not present in sections examined.

Lymph nodes (Missing)

Liver Focus of hypertrophic hepatocytes.

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Kidneys Moderate foci of interstitial mononuclear cells.

Urinary bladder (Missing)

Stomach Foci of submucosal adipose tissue(g).

Caecum Minimal lymphoid hyperplasia.
Colon Minimal lymphoid hyperplasia.

The following tissues were considered normal:
Aorta, Trachea, Heart, Spleen, Pancreas, Uterus, Ovaries, Thyroids, Adrenals,
Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Skeletal
muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

85 mg/kg/day

Rat No./Sex: R 472 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Minimal pneumonitis. Minimal bronchiolar epithelial

hypertrophy with prominent goblet cells. Minimal peribronchical lymphoid aggregates. Minimal peribronchical acini with inflammation. Moderate

alveolar haemorrhage. Minimal alveolar oedema.

Lymph nodes (Missing)
Liver (Missing)
Liver Perls' (Missing)

Spleen (Missing)
Spleen Perls' (Missing)

Pancreas Minimal focal exocrine acinar atrophy.

Uterus Moderate dilatation of lumen.

Ovaries No corpora lutea.

Pituitary (Missing)
Duodenum (Missing)
Jejunum (Missing)
Ileum (Missing)
Caecum (Missing)
Colon (Missing)

The following tissues were considered normal:

Aorta, Heart, Kidneys, Urinary bladder, Thyroids, Adrenals, Salivary gland, Oesophagus, Stomach, Skeletal muscle, Byes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

TTF 282

Level:

85 mg/kg/day

Rat No./Sex: R

Designated:

TERMINAL

473 /F

The following observations were noted:

Trachea

(Missing)

Lungs

Minimal bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal peribronchiolar

lymphoid aggregates.

Liver Perls'

Trace of centrilobular Perls' positive material.

Spleen Perls'

Moderate Perls' positive material.

Kidneys

Minimal foci of interstitial mononuclear cells.

Ovaries

Cystic follicle(s).

The following tissues were considered normal:

Aorta, Heart, Lymph nodes, Liver, Spleen, Pancreas, Urinary bladder, Uterus, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Eyes, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 474 /F

Designated: TERMINAL

The following observations were noted:

Lungs Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates. Moderate alveolar haemorrhage.

Lymph nodes (Missing)

Liver Minimal foci of mononuclear cells. Minimal bile duct

hyperplasia. Early fibrous bridging.

Spleen Perls' Moderate Perls' positive material.

Ovaries No corpora lutea.

Stomach Foci of submucosal adipose tissue(g).

Caecum Minimal lymphoid hyperplasia.

Eyes (Missing)

The following tissues were considered normal:
Aorta, Trachea, Heart, Liver Perls', Spleen, Pancreas, Kidneys, Urinary
bladder, Uterus, Thyroids, Adrenals, Pituitary, Salivary gland, Cesophagus,
Duodenum; Jejunum, Ileum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

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(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: TTF 282

Level: 85 mg/kg/day

Rat No./Sex: R 477 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent

goblet cells. Minimal pneumonitis.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Duodenum (Missing)
Jejunum (Missing)
Ileum (Missing)
Caecum (Missing)
Colon (Missing)
Eyes (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 478 /F

Designated: TERMINAL

The following observations were noted:

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Minimal pneumonitis. Moderate foci of

pigmented macrophages.

Liver (Missing)
Liver (Missing)
Liver Perls' (Missing)

Spleen Perls' Moderate Perls' positive material.

Pancreas Minimal focal exocrine acinar atrophy.

Stomach Foci of submucosal adipose tissue(g).

Eyes (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Spleen, Kidneys, Urinary bladder, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

Date: 24 Oct85

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(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 479 /F

Designated: TERMINAL

The following observations were noted:

Aorta	(Missing)
Trachea	(Missing)
Lungs	(Missing)
Lymph nodes	(Missing)
Liver Perls'	Trace of centrilobular Perls' positive material.
Spleen Perls'	Moderate Perls' positive material.
Pancreas	(Missing)
Kidneys	Peripelvic lymphoid aggregates.
Urinary bladder	(Missing)
Uterus	(Missing)
Ovaries	(Missing)
Thyroids	(Missing)
Pituitary	(Missing)
Salivary gland	(Missing)
Oesophagus	(Missing)
Caecum	(Missing)
Skeletal muscle	(Missing)
Eyes	(Missing)
Spinal cord	(Mussing)
Brain	(Missing)
Sternum	(Missing)

The following tissues were considered normal: Heart, Liver, Spleen, Adrenals, Stomach, Duodenum, Jejunum, Ileum, Colon.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 480 /F

Designated: TERMINAL

The following observations were noted:

Aorta (Missing)
Trachea (Missing)
Lungs (Missing)
Lymph nodes (Missing)
Liver (Missing)
Liver Perls' (Missing)

Spleen Perls' Moderate Perls' positive material.

Pancreas (Missing)

Kidneys Focus of dilated cortical tubules with eosinophilic

contents.

Urinary bladder (Missing)
Uterus (Missing)
Ovaries (Missing)
Thyroids (Missing)
Pituitary (Missing)
Salivary gland (Missing)
Oesophagus (Missing)

Stomach Foci of submucosal adipose tissue(g).

Caecum Minimal lymphoid hyperplasia.

Skeletal muscle (Missing)
Eyes (Missing)
Spinal cord (Missing)
Brain (Missing)
Sternum (Missing)

The following tissues were considered normal: Heart, Spleen, Adrenals, Duodenum, Jejunum, Ileum, Colon.

Pathologist: L.E.Fish

<u>Date</u>: 24 Oct85

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 481 /F

Designated: TERMINAL

The following observations were noted:

Lungs Minimal pneumonitis. Minimal peribronchiolar lymphoid

aggregates. Moderate foci of pigmented macrophages.

Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Moderate Perls' positive material.

Pancreas (Missing) Urinary bladder (Missing)

Stomach Foci of submucosal adipose tissue(g).

Eyes (Missing)

The following tissues were considered normal:

Aorta, Trachea, Heart, Liver, Spleen, Kidneys, Uterus, Ovaries, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum, Caecum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 483 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Moderate peribronchiolar lymphoid aggregates. Moderate

bronchiolar epithelial hypertrophy with prominent goblet cells. Moderate peribronchiolar acini with

inflammation. Minimal pneumonitis.

Lymph nodes Abscess.

Liver Minimal vacuolated hepatocytes.

Spleen Perls' Marked Perls' positive material.

Ovaries No corpora lutea.

Addrenals Focus of vacuolated cortical cells.

Stomach Foci of submucosal adipose tissue(g).

Eyes (Missing)

The following tissues were considered normal:
Aorta, Heart, Liver Perls', Spleen, Pancreas, Kidneys, Urinary bladder, Uterus,
Thyroids, Pituitary, Salivary gland, Oesophagus, Duodenum, Jejunum, Ileum,
Caecum, Colon, Skeletal muscle, Spinal cord, Brain, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 484 /F

Designated: TERMINAL

The following observations were noted:

Aorta (Missing)
Trachea (Missing)

Lungs Minimal peribronchiolar lymphoid aggregates. Minimal

foci of pigmented macrophages. Foci of alveolar

haemorrhage.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Pancreas (Missing)

Kidneys Minimal foci of dilated cortical tubules with

eosinophilic contents.

Urinary bladder (Missing)
Uterus (Missing)
Ovaries (Missing)
Thyroids (Missing)
Pituitary (Missing)
Salivary gland (Missing)
Oesophagus (Missing)

Stomach Foci of submucosal adipose tissue(g).

· Colon Minimal lymphoid hyperplasia.

Skeletal muscle (Missing)
Eyes (Missing)
Spinal cord (Missing)
Brain (Missing)
Sternum (Missing)

The following tissues were considered normal:

Heart, Liver, Liver Perls', Spleen, Adrenals, Duodenum, Jejunum, Ileum, Caecum.

Pathologist: L.E.Fish

(Pathology - continued)

IPO/26/27

Individual Animal Histopathology

Compound: FTF 282

Level: 85 mg/kg/day

Rat No./Sex: R 487 /F

Designated: TERMINAL

The following observations were noted:

Trachea Minimal subepithelial inflammation.

Lungs Munimal pneumonitis. Minimal bronchiolar epithelial

hypertrophy with prominent goblet cells. Minimal

peribronchiolar lymphoid aggregates.

Lymph nodes (Missing)

Spleen Perls' Moderate Perls' positive material.

Kidneys Minimal foci of dilated cortical tubules with

eosinophilic contents.

Ovaries No corpora lutea.

Colon Minimal lymphoid hyperplasia.

Eyes (Missing)
Spinal cord (Missing)
Brain (Missing)

The following tissues were considered normal:

Aorta, Heart, Liver, Liver Perls', Spleen, Pancreas, Urinary bladder, Uterus, Thyroids, Adrenals, Pituitary, Salivary gland, Oesophagus, Stomach, Duodenum, Jejunum, Ileum, Caecum, Skeletal muscle, Sternum.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound: ITF 282

Level: 85 mg/kg/day

Rat No./Sex: R 489 /F

Designated: TERMINAL

The following observations were noted:

Aorta (Missing)
Trachea (Missing)
Lungs (Missing)
Lymph nodes (Missing)

Liver Perls' Trace of centrilobular Perls' positive material.

Spleen Perls' Marked Perls' positive material.

Pancreas (Missing)

Kidneys Minimal foci of interstitial mononuclear cells. Focus

of dilated cortical tubules with eosinophilic

contents.

Urinary bladder (Missing) Uterus (Missing) Ovaries (Missing) Thyroids (Missing) Pituitary (Missing) Salivary gland (Missing) (Missing) Oesophagus Skeletal muscle (Missing) Eyes (Mussing) Spinal cord (Missing) Brain (Missing) Sternum (Missing)

The following tissues were considered normal:

Heart, Liver, Spleen, Adrenals, Stomach, Duodenum, Jejunum, Ileum, Caecum,

Colon.

Pathologist: L.E.Fish

(Pathology - continued)

IFO/26/27

Individual Animal Histopathology

Compound:

ITF 282

Level:

85 mg/kg/day

Rat No./Sex: R

490 /F

Designated:

Colon

TERMINAL

The following observations were noted: Aorta (Missing)

Trachea	(Missing)
Lungs	(Missing)
Lymph nodes	(Missing)
Liver Perls'	Trace of centrilobular Perls' positive material.
Spleen Perls'	Moderate Perls' positive material.
Pancreas	(Missing)
Urinary bladder	(Missing)
Uterus	(Missing)
Ovaries	(Missing)
Thyroids	(Missing)
Pituitary	(Missing)
Salivary gland	(Missing)
Oesophagus	(Missing)

Stomach Foci of submucosal adipose tissue(g).

Caecum Minimal mucosal inflammation. Minimal submucosal

inflammation. Minimal submucosal oedema.

Minimal mucosal inflammation. Minimal submucosal

inflammation.

Skeletal muscle (Missing) Eyes (Missing) Spinal cord (Missing) Brain (Missing) Sternum (Missing)

The following tissues were considered normal:

Heart, Liver, Spleen, Kidneys, Adrenals, Duodenum, Jejunum, Ileum.

Pathologist: L.E.Fish